REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

I. Status of Claims and Formal Matters

Claims 1, 3-17, 20, 21, 28-32, 45-69, and 93 are currently pending and under consideration in this application. Claims 2, 18, 19, 22-27, 33-44, 70-78, 80-92, and 94 are canceled. Claims 3, 4, 7, 10, 12, 13, 15 and 30 have been amended to respond to Examiner's claim objections as being improper in form. Support for the claim amendments is found throughout the specification as originally filed. The Examiner is thanked for indicating that SEQ ID NO: 2 is free of the prior art. New claims 95 and 96 specify that the sequence of lineage I WNV cDNA is according to either SEQ ID NOs 1 or 2. Support for new claims 95 and 96 can be found for example in Figure 21. No new matter has been added by this amendment.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

II. The Objections Under 37 C.F.R. § 1.75(c) Are Overcome

The Examiner objected to claims 3-17, 20, 21, and 28-31 as being in improper form because a multiple dependent claim cannot depend from a multiple dependent claim. Claims 3, 4, 7, 10, 12, 13, 15 and 30 have been amended to place the objected to claims into proper form.

Accordingly, reconsideration and withdrawal of these rejections are respectfully requested.

III. The Rejections Under 35 U.S.C. § 102 Are Overcome

Claim 1 is rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Chambers *et al.* The Examiner asserts that Chambers *et al.* teaches the use of reverse genetics systems to create chimeric flaviviruses that can induce neutralizing antibodies and be used for screening and identifying antiflaviviral compounds.

Claim 1 is also rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Lai *et al.* The Examiner asserts that Lai *et al.* teaches reverse genetics systems and attenuated backbones to construct chimeric flaviviruses for DEN-4 that can be used in screening and identifying antiflavivirual compounds.

Claim 1 is also rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Yamshchikov *et al.* The Examiner asserts that Yamshchikov *et al.* teaches reverse genetic systems and a replicon of WNV that can be used in screening and identifying antiflaviviral compounds. Applicant respectfully disagrees and traverses the rejection.

It is respectfully pointed out that a two-prong inquiry must be satisfied in order for a Section 102 rejection to stand. First, the prior art reference must contain all of the elements of the claimed invention. *See Lewmar Marine Inc. v. Barient Inc.,* 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987). Second, the prior art must contain an enabling disclosure. *See Chester v. Miller,* 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990). A reference contains an enabling disclosure if a person of ordinary skill in the art could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself in possession of the invention. *See In re Donohue*, 226, U.S.P.Q. 619, 621 (Fed. Cir. 1985).

Applying the law to the instant facts, the references relied upon by the Office Action do not disclose, suggest or enable Applicants' invention.

Chambers involves construction of chimeric yellow fever/Japanese encephalitis (YF/JE) viruses from cDNA templates encoding various structural proteins. Chambers suggests that the chimeric viruses could potentially be useful as live-attenuated vaccine candidates and also for studying protein-protein and RNA-protein interactions important for flavivirus replication and pathogenesis. Chambers does not disclose or suggest using the chimeric YR/JE viruses for screening or identifying antiflaviviral compounds.

Lai involves the construction of dengue type 4 virus cDNA, yielding infectious RNA transcripts, to provide a new approach to the development of safe and effective dengue vaccines. Lai does not disclose or suggest that such chimers are useful for screening and/or identifying antiflaviviral compounds.

Yamshchikov involves a full-length infectious clone of the lineage II WN strain used to investigate effects of insertion of 5'-end and 3'-end nonrelated sequences on virus replication

and infectivity of synthetic RNA. Yamshchikov does not disclose or suggest that such replicons are useful for screening and/or identifying antiflaviviral compounds.

Contrary to the assertions in the Office Action, none of the cited references disclose or suggest using a reverse genetics system to screen for or identify antiflaviviral compounds. Chambers, at p. 3095, provides an approach of engineering chimeric YF/JE viruses in which the structural proteins prM and E of JE virus were exchanged for the homologous proteins of YF virus within a molecular clone of the YF17D strain. The reference provides that this approach "is relevant for the potential use of recombinant flaviviruses as live-attenuated vaccine candidates and also for studying protein-protein and RNA-protein interactions important for flavivirus replication and pathogenesis."

Therefore, there is no teaching or suggestion in any of the cited references of a system for screening and identifying antiflaviviral compounds, or antiviral therapy. Instead, the cited references relate to systems that are useful for analyses of viral replication and pathogenesis.

Accordingly, reconsideration and withdrawal of the Section 102 rejections are earnestly requested.

IV. The Rejections Under 35 U.S.C. § 103 Are Overcome

The first two obviousness rejections are collectively addressed and respectfully traversed. The cited references do not render the instant invention obvious.

(1) Claims 1, 32, 59, 61, 62, and 66 are rejected under 35 U.S.C. §103(a) as being unpatentable over Shi *et al.* in view of Hicks. The Office Action asserts that Shi *et al.* teaches a plasmid with a cDNA sequence corresponding to the West Nile virus lineage I comprising a T7 promoter sequence and IFA to detect expression. Furthermore the Examiner asserts that Shi *et al.* teaches a DNA sequence encoding a full length and fully infectious mRNA of WNV lineage I having a 5' and 3' end with a promoter. Shi allegedly does not teach the use of a reporter gene such as GFP, however the Office Action asserts that because Hicks allegedly teaches the use of GFP to monitor nucleic acid transcription of viral genomes, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the DNA sequence of Shi and the GFP of Hicks because Hicks teaches that GFP permits detection of viral expression without the need to wait for overt cytopathic effect or for fixing cells. Moreover, the Examiner asserts that one of ordinary skill in the art at the time the invention was made would have had a

reasonable expectation of success for using the DNA sequence of Shi and the GFP of Hicks because both Shi and Hicks teach nucleic acid transcription.

(2) Claims 67, 68, 69 are rejected under 35 U.S.C. §103(a) as being unpatentable over Shi *et al.* and Hicks in view of Khromykh *et al.* The Examiner asserts that Khromykh teaches the use of two reporters (neomycin and CAT) controlled by an IRES to monitor transcription in host cells as well as to enable selection of host cells expressing desired proteins. The Examiner asserts that one of ordinary skill in the art at the time the invention was made would have been motivated to combine the DNA sequence and GFP of Shi at al. and Hicks and the second reporter wherein both reporters are optionally preceded by an IRES of Khromykh because Khromykh teaches the addition of a second reporter to enable selection of host cells containing desired proteins.

Initially, it is submitted that Shi *et al.* is not a prior art document. Attached hereto is a Declaration under 35 C.F.R. §1.132 (hereinafter "Declaration"). The Declaration is presently signed by Pei-Yong Shi, Mark Tilgner, and Michael K. Lo. The Declaration states that Shi *et al.* is not the work of others as defined by 35 U.S.C. §102(a). The Declaration is sufficient to overcome the grounds of rejection of claims 1, 32, 59, 61, 62, and 66 under 35 U.S.C. §103(a) because the Declaration clearly states that co-authors Kim A. Kent, and Kristen A. Bernard did not make an independent inventive contribution to the invention claimed in this application. Should the rejection be maintained, the Examiner is requested to indicate how the Declaration fails to successfully overcome the grounds of rejection.

Moreover, it is respectfully submitted that it is well-settled that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further still, "obvious to try" is not the standard under 35 U.S.C. §103. *In re Fine,* 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). And, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." Also, the Examiner is respectfully reminded that for the Section 103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Assuming arguendo that Shi could be considered prior art, contrary to the assertions in the Office Action, there is no teaching or suggestion in Shi or Hick, to use a reporter molecule to indicate transcription of a full-length cDNA molecule encoding lineage I WNV. Simply, there is no motivation to combine Shi and Hicks. Applicants could have selected to use various other reporter molecules besides GFP.

Moreover, even if, as alleged, Hicks states that "GFP permits detection of viral expression without need to wait for overt cytopathic effect or for fixing cells," this is irrelevant because expression alone is not enough for use of the replicons according to the present invention. The present invention requires high levels of a RNA transcript from WNV cDNA clone that is highly infectious. Indeed, according to the present invention, replication is permitted up to 48 hours (see Figure 10). Hicks, on the other hand, involves introducing GFP into virus genomes for studies of virus cell-to-cell spread, or, the dynamic process of viral infection.

Hicks also involves insertion of GFP into different regions of the genome. On page 298, Hicks discusses the approaches used to introduce GFP to investigate the mechanisms of viral transport: (1) by fusing GFP with another viral protein in order to study the function or intracellular trafficking of that protein; and (2) inserting EGFP (enhanced GFP) into the 3' end prior to the nucleocapsid gene. The present invention, on the other hand, teaches insertion of GFP into the 3' untranslated region of WNV at the *Nsi*I site.

Thus Hicks cannot be said to make the present claims obvious.

Furthermore, one of skill in the art is aware of many difficulties encountered during flaviviral cloning. For example, Shi points out on page 5847, first full paragraph:

> Infectious full-length cDNA clones for a number of flaviviruses have been successfully developed for the study of viral replication and pathogenesis. In several cases, assembly of full-length flavivirus clones in a plasmid vector was not straightforward because clones containing large portions of the genome were unstable and deleterious for bacterial hosts.

And, Bredenbeek reports[1]:

[1] Bredenbeek, PJ, Kooi, EA, Lindenbach, B, Huijkman, N, Rice, CM, and Spaan, WJM: A stable full-length yellow fever virus cDNA clone and the role of conserved RNA elements in flavivirus replication. J. Gen. Vir. (2003) 84: 1261-1268, at 1262, (citing Rice *et al.*, 1989).

> Attempts to construct a stable, full-length infectious YF cDNA in E. coli plasmid and λ phage vectors have been unsuccessful due [to] problems with the genetic stability of the full-length clone in the prokaryotic host.

Thus it is respectfully submitted that one of skill in the art would expect that ANY insertions, deletions, or variations in the genome of a flavivirus may create difficulties with expression, stability, or infectivity of resultant RNA in a reverse genetics system.

For all of the reasons stated above, there is no motivation for one of skill in the art to combine Shi with Hicks to arrive at the present invention.

Moreover, Applicants demonstrated the use of a second reporter preceded by IRES. Figure 8 depicts construction of replicons comprising GFP and Neo reporter gene fragments, along with an upstream IRES regulatory sequence engineered into the 3' untranslated region of WNV. Neither Shi nor Hicks teaches or suggests WNV replicons comprising two reporter molecules, further comprising IRES.

Khromykh does nothing to correct this deficiency.

First, Khromykh involves an entirely different system: subgenomic replicons. As noted in Shi *et al.*[2], subgenomic replicon systems are an entirely different reverse genetic system than full-length infectious cDNA clones. Page 960, left column, provides:

> Two types of systems are commonly used, full-length infectious cDNA clones and subgenomic replicons. For the infectious cDNA clone system, the full-length cDNA of the genome RNA is incorporated into a plasmid under the control of a T7 or SP6 promoter, and stably amplified in Escherichia coli. RNA transcribed from the full-length cDNA clone is highly infectious upon transfection into permissive cells, resulting in progeny virus

Further, on page 961, bottom of first paragraph:

[2] Shi, P.: Genetic systems of West Nile virus and their potential applications. Current Op. Invest. Drugs (2003) 4(8): 959-965.

> Subgenomic replicons contain deletions of regions not essential for viral replication, and are capable of replicating autonomously in permissive host cells.

Therefore, even if, as the Office Action alleges, Khromykh teaches the addition of a second reporter to enable selection of host cells containing desired proteins in the system used therein, wherein both reporters are optionally preceded by an IRES, the subgenomic replicon system cannot be said to motivate or suggest one of skill in the art to arrive at the full-length infectious cDNA clone system of the present invention.

Second, Khromykh relates an entirely different flavivirus, Kunjin. It is respectfully submitted that in addition to the difficulties in cloning flaviviruses addressed above, one of skill in the art is aware of the differences amongst flaviviruses that prevent extrapolation of results from one flavivirus to another. And, as discussed, one of skill in the art would expect that any insertions, deletions, or variations in the genome of a flavivirus may create difficulties with expression, stability, or infectivity of resultant RNA in a reverse genetics system. Therefore, there is no reasonable expectation of successful incorporation of an IRES-Neo cassette into the 3'UTR of WNV based on the cited references.

Third, Kromykh relates to insertion of CAT and Neo reporter genes, whereas the present invention teaches Neo and luciferase or Neo and GFP. Thus Khromykh does not teach or suggest the DNA molecules in claims 67-69 either alone or in combination with Shi and Hicks.

Thus it would not have been obvious to extend the results of Shi, and Hicks in view of Khromykh to arrive at the present invention.

For all of the reasons stated above, there is no motivation for one of skill in the art to combine Shi with Hicks in view of Khromykh to arrive at the present invention.

Applicants also remind the Examiner that it is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicant's structure as a template, and selecting elements from references to fill in the gaps. *Interconnect Planning*, 744 F.2d 1132, 1143 (Fed. Cir. 1985). Applicants believe that only through the exercise of impermissible hindsight have the cited references been selected and relied upon by the Office. There is no teaching or suggestion in the cited art to motivate one of ordinary skill in the art to combine elements of the references to result in the presently claimed invention.

Accordingly, reconsideration and withdrawal of the first and second Section 103 rejections are earnestly requested.

The next two obviousness rejections (3 and 4) are collectively addressed and respectfully traversed. The cited references do not render the instant invention obvious.

(3) Claims 1, 32, 45, 50, 51, 54, 55, 57, and 93 are rejected under 35 U.S.C. §103(a) as being unpatentable over Khromykh *et al.* in view of Chambers *et al.* supported by Barrett. The Examiner asserts that Khromykh teaches replicons of the Kunjin virus containing large deletions in the structural region encompassing the envelope protein with a CAT reporter gene. The Examiner further asserts that Khromykh also teaches the use of a second reporter controlled by an IRES as well as expression in host cells. The Examiner also asserts that Khromykh teaches that Kunjin virus is closely related to West Nile as members of the flavivirus family, and that it teaches the use of the replicons for flaviviral RNA replication as well as a RNA virus expression system. Moreover, the Examiner notes that Khromykh does not teach the T7 promoter, as recited in claim 54, but asserts that the presence of a promoter to induce transcriptions is inherently included in said replicons and further, that one of ordinary skill in the art would know to substitute a T7 promoter as they are functional equivalents. Additionally, although Khromykh allegedly does not teach the WNV lineage I replicon, the Examiner asserts that the presence of a promoter to induce transcriptions is inherently included in said replicons. The Examiner further asserts that one of ordinary skill in the art would know to substitute a T7 promoter for another promoter as they are functional equivalents. Moreover, the Office Action states that Chambers teaches a reverse genetics system using the ChimeriVax platform, wherein the premembrane and envelope protein genes are deleted and substituted with those of other flaviviruses to create cDNAs encoding for chimeric viruses. Chambers allegedly teaches that the flaviviruses envelope regions can be deleted and replaced with the envelope regions of other flaviviruses. Moreover, that Barrett in support of Chambers states that the ChimeriVax technology can be applied to WNV. This is allegedly further supported by Lai and Yamshikov. The Examiner asserts that one of ordinary skill in the art would have been motivated to combine the flaviviral DNA molecule with a structural protein deletion of Khromykh *et al.* in the WN reverse genetics system of Chambers supported by Barrett because Chambers supported by Barrett teaches that the reverse genetics system can be used for other structurally similar

flaviviruses such as WN since flaviviruses are sufficiently structurally related for purposes of reverse genetics applications.

(4) Claims 47, 48, 56, and 58 are rejected under 35 U.S.C. §103(a) as being unpatentable over Khromykh *et al.* and Chambers *et al.* supported by Barrett in view of Hicks. The Examiner asserts that one of ordinary skill in the art would have been motivated to combine the reverse genetics system of Khromykh and Chambers supported by Barrett and the GFP of Hicks because Hicks teaches that the GFP reporter gene permits detection of viral expression without the need to wait for overt cytopathic effect or for fixing cells. Moreover, the Examiner asserts that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for using the reverse genetics system of Khromykh and Chambers supported by Barrett and the GFP of Hicks because Khromykh and Chambers supported by Barrett and Hicks both teach nucleic acid transcription.

It is respectfully submitted that it is well-settled that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further still, "obvious to try" is not the standard under 35 U.S.C. §103. *In re Fine,* 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). And, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." Also, the Examiner is respectfully reminded that for the Section 103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

Applying the law to the instant facts, the references relied upon by the Office Action do not disclose, suggest, or enable Applicants' invention. To establish *prima facie* obviousness of a claimed invention, each of the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974); also MPEP 2143.03. It is respectfully submitted that Khromykh, Chambers, Barrett, and Hicks do not, either alone or in combination, teach or suggest each and every element of the claimed invention.

First, as discussed previously, none of the cited references teach or suggest a reverse genetics system *for screening and identifying antiflaviviral compounds* as recited in claim 1.

Second, as discussed above, Khromykh relates an entirely different flavivirus, Kunjin, not WNV. It is respectfully asserted that it is improper to extrapolate the results of a study of one virus to another simply because both viruses are members of the same family. Morover, Khromykh involves different reporter genes, which as discussed above, may affect expression, stability, or infectivity of resultant RNA in a reverse genetics system.

Third, Chambers also relates to entirely different flaviviruses, namely Yellow Fever (YF) and Japanese Encephalitis (JE). The authors genetically engineered chimeric YF/JE viruses in which the structural proteins prM and E of JE virus were ***exchanged*** for the homologous proteins of YF virus within a molecular clone. Specifically, the premembrane and envelope protein genes are ***deleted and substituted with those of other flaviviruses*** to create cDNAs encoding for chimeric viruses. Chambers allegedly teaches that the flaviviruses envelope regions can be deleted and replaced with the envelope regions of other flaviviruses. This is NOT what is taught by the present invention in claims 45, 50, 51, 54, 55, 57, or 93. Instead, the claims recite to a DNA molecule comprising a DNA sequence encoding mRNA of a lineage I WNV genome...wherein said DNA molecule comprises a ***deletion*** in said DNA sequence corresponding to one or more structural genes of said lineage I WNV genome. Unlike the chimer in Chambers, the chimers of the present invention simply do not contain a replacement for the structural gene deletions. Thus because the reverse genetic engineering approach in Chambers is completely different and involves different flaviviruses, it cannot be said to make the present claims obvious.

Fourth, Barrett reports that the technology of Chambers "[has been demonstrated to have applicability] for a number of flaviviruses, including, potentially, West Nile Virus." But as just discussed, the technology of Chambers is different from and cannot be extrapolated to the technology of the present invention to make the present claims obvious.

Fifth, as previously discussed, Hicks does not teach or suggest the introduction of GFP into any WNV genome in order to construct a stable, full-length infectious WNV cDNA. And, as discussed above, taking into consideration the difficulties encountered in cloning flaviviruses, one of skill in the art would have no expectation of success.

For all of the reasons stated above, there is no motivation for one of skill in the art to combine Khromykh and Chambers supported by Barrett in view of Hicks.

Applicants also remind the Examiner that it is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicant's structure as a template, and selecting elements from references to fill in the gaps. *Interconnect Planning*, 744 F.2d 1132, 1143 (Fed. Cir. 1985). Applicants believe that only through the exercise of impermissible hindsight have the cited references been selected and relied upon by the Office. There is no teaching or suggestion in the cited art to motivate one of ordinary skill in the art to combine elements of the references to result in the presently claimed invention.

Accordingly, reconsideration and withdrawal of the Section 103 rejections are earnestly requested.

The next three obviousness rejections (5-7) are collectively addressed and respectfully traversed. The cited references do not render the instant invention obvious.

(5) Claims 1, 32, and 59 are rejected under 35 U.S.C. §103(a) as being unpatentable over Hurrelbrink *et al.* in view of Chambers *et al.* supported by Barrett. Hurrelbrink allegedly teaches a plasmid with a genome length cDNA sequence corresponding to Murray Valley virus of the flavivirus family comprising a T7 promoter sequence. The Examiner notes that Hurrelbrink does not teach the plasmid with a genome length cDNA sequence corresponding to WNV, however he asserts that one of ordinary skill in the art would have been motivated to combine the genome-length flavivirus cDNA sequence of Hurrelbrink *et al.* and the WN reverse genetics system of Chambers supported by Barrett because Chambers supported by Barrett teaches that the reverse genetics system can be used for other structurally similar flaviviruses such as WN since flaviviruses are sufficiently structurally related for purposes of reverse genetics applications. Moreover, it is asserted that one of ordinary skill in the art would have had a reasonable expectation of success for using the genome-length flavivirus cDNA sequence of Hurrelbrink and the WN reverse genetics system of Chambers supported by Barrett because Hurrelbrink and Chambers supported by Barrett both teach the use of reverse genetics systems.

(6) Claims 61, 62, and 66 are rejected under 35 U.S.C. §103(a) as being unpatentable over Hurrelbrink *et al.* and Chambers *et al.* supported by Barrett in view of Hicks. The Examiner notes that Hurrelbrink and Chambers supported by Barrett does not teach the use of a reporter gene such as GFP, however he asserts that one of ordinary skill in the art would have been motivated to combine the genome cDNA sequence of Hurrelbrink and Chambers supported by Barrett and the GFP of Hicks because Hicks teaches that GFP reporter gene permits detection

of viral expression without the need to wait for overt cytopathic effect or for fixing cells. Moreover, that one of ordinary skill in the art would have had a reasonable expectation of success for using the cDNA sequence of Hurrelbrink and Chambers supported by Barrett and the GFP of Hicks because Hurrelbrink and Chambers supported by Barrett and Hicks both teach nucleic acid transcription.

(7) Claims 67, 68, and 69 are rejected under 35 U.S.C. §103(a) as being unpatentable over Hurrelbrink *et al.*, Chambers *et al.* supported by Barrett, Hicks in view of Khromykh *et al.* The Examiner notes that Hurrelbrink and Chambers supported by Barrett and Hicks do not teach the use of a second reporter gene wherein the first and second reporter gene are preceded by an IRES to facilitate translation. However, the Examiner asserts that Khromykh teaches the use of two reporters, CAT and neomycin, controlled by IRES to monitor transcription in host cells as well as to enable selection of host cells expressing desired proteins. Moreover, that one of ordinary skill in the art at the time the invention was made would have been motivated to combine the DNA sequence and GFP of Hurrelbrink and Chambers supported by Barrett and Hicks and the second reporter and IRES of Khromykh because Khromykh teaches the addition of a second reporter to enable selection of host cells containing desired proteins. Further, that one or ordinary skill in the art would have had a reasonable expectation of success for using the DNA sequence and GFP of Hurrelbrink and Chambers supported by Barret and Hicks and the second reporter and IRES of Khromykh because Hurrelbrink and Chambers supported by Barrett and Hicks and Khromykh both teach nucleic acid transcription.

The Examiner is respectfully directed to the case law, namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." For the §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicant's disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

Applying the law to the instant facts, the reference relied upon by the Office Action does not disclose, suggest or enable Applicant's invention.

As discussed above, it would not have been obvious to extend the results of Chambers, Barrett, Hicks, and Khromykh, either alone or in combination, to arrive at the present invention.

Hurrelbrink does not cure the defect. Hurrelbrink relates to construction of a stable genome-length cDNA infectious clone. The Examiner asserts that one of skill in the art would have been motivated to combine Hurrelbrink with Chambers to arrive at the full-length cDNA infectious clone of the present invention. However, as discussed above, Chambers involves a deletion and substitution of premembrane and envelope protein genes. Therefore, combining Hurrelbrink with Chambers alone would have led one of skill in the art to arrive at a different cDNA clone. Moreover, as discussed above, it is inappropriate to extrapolate the construction of one flavivirus to another when one considers the difficulties encountered in cloning flaviviruses. Therefore, it cannot be said that one of skill in the art would have an expectation of success.

For all of the reasons stated above, there is no motivation for one of skill in the art to combine Hurrelbrink, Chambers, Barrett, Hicks, and Khromykh either alone or in any combination thereof to arrive at the present invention.

Applicant reminds the Examiner that it is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicant's structure as a template, and selecting elements from references to fill in the gaps. *Interconnect Planning*, 744 F.2d 1132, 1143 (Fed. Cir. 1985). Applicant believes that only through the exercise of impermissible hindsight have the cited references been selected and relied upon by the Office. There is no teaching or suggestion in the cited art to motivate one of ordinary skill in the art to combine elements of the references to result in the presently claimed invention.

Consequently, reconsideration and withdrawal of the Section 103 rejections are earnestly requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested and the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

Reconsideration and withdrawal, or modification of the restriction requirement, and a prompt and favorable examination on the merits, is respectfully requested.

Respectfully submitted,

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